

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

GLAXOSMITHKLINE
Corporate Intellectual Property
Attn. Goddard, Carolyn
CN925.1
980 Great West Road
Brentford, Middlesex TW8 9GS
UNITED KINGDOM

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

08 JUL 2005

(PCT Rule 44.1)

Date of mailing
(day/month/year)

07/07/2005

Applicant's or agent's file reference

CJG/PB60780

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/GB2005/000939

International filing date
(day/month/year)

10/03/2005

Applicant

GLAXO GROUP LIMITED

07 JUL 2005

1. ☒ The applicant is hereby notified that the International Search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Isabel Delgado Barajas

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CJG/PB60780	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/GB2005/000939	International filing date (<i>day/month/year</i>) 10/03/2005	(Earliest) Priority Date (<i>day/month/year</i>) 12/03/2004	
Applicant GLAXO GROUP LIMITED			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

BENZAZEPINE DERIVATIVES FOR THE TREATMENT OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

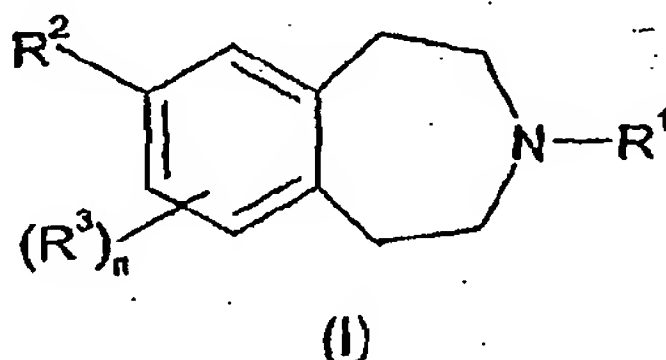
INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB2005/000939

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to novel benzazepine derivatives of formula (I) :



wherein:

R^1 represents $-C_{3-7}$ cycloalkyl optionally substituted by C_{1-3} alkyl;

R^2 represents -aryl, -heterocyclyl, -heteroaryl, -aryl-X- C_{3-8} cycloalkyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X- C_{3-8} cycloalkyl, -heteroaryl-X-aryl, -heteroaryl-X-heteroaryl, -heteroaryl-X-heterocyclyl, -heterocyclyl-X- C_{3-8} cycloalkyl, -heterocyclyl-X-aryl, -heterocyclyl-X-heteroaryl or -heterocyclyl-X-heterocyclyl;

X represents a bond, O, CO, $-CH_2O-$, $-COCH_2-$, $-COCH_2O-$, $-CONR^{2b}-$, $-COCH_2NR^{2b}CO-$, $-CSNH-$, SO_2 , $-SO_2C_{1-3}$ alkyl-, $-SO_2C_{2-3}$ alkenyl-, $-COC_{2-3}$ alkenyl-, $-CO-C(R^{2a})(R^{2b})-$ or $-CO-$

$C(R^{2a})(R^{2b})CH_2-$; having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB2005/000939

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D223/16 C07D405/12 C07D401/12 C07D417/12 C07D409/12
 C07D413/12 C07D403/12 C07D495/04 C07D409/14 C07D513/04
 C07D471/04 C07D413/04 C07D401/04 C07D405/04 C07D417/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/05194 A (DR. KARL THOMAE GMBH) 22 February 1996 (1996-02-22) page 76; compound (9) page 93; example 10	1
X	EP 0 612 741 A (DR. KARL THOMAE GMBH) 31 August 1994 (1994-08-31) page 45; compounds (29),(31)	1
A	WO 2004/018432 A (ELI LILLY AND COMPANY; GADSKI, ROBERT, ALAN; HIPSKIND, PHILIP, ARTHUR;) 4 March 2004 (2004-03-04) cited in the application page 39; example 32 page 37; example 20 page 1 claims 9-15	1,3

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

17 June 2005

Date of mailing of the international search report

07/07/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/000939

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/000939

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2005/000939

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9605194	A	22-02-1996	DE 4429079 A1	22-02-1996
			AU 3345995 A	07-03-1996
			CA 2197789 A1	22-02-1996
			WO 9605194 A1	22-02-1996
			EP 0777667 A1	11-06-1997
			JP 10504298 T	28-04-1998
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EP 0612741	A	31-08-1994	DE 4305388 A1	25-08-1994
			DE 4332168 A1	23-03-1995
			AT 167185 T	15-06-1998
			AU 673875 B2	28-11-1996
			AU 5632494 A	25-08-1994
			BR 1100484 A3	01-08-2000
			CA 2116068 A1	23-08-1994
			CN 1099755 A ,C	08-03-1995
			CZ 9400374 A3	15-12-1994
			DE 59406157 D1	16-07-1998
			DK 612741 T3	29-03-1999
			EP 0612741 A1	31-08-1994
			ES 2118992 T3	01-10-1998
			FI 940806 A	23-08-1994
			HU 70768 A2	30-10-1995
			IL 108733 A	04-01-1998
			JP 3545446 B2	21-07-2004
			JP 6256343 A	13-09-1994
			MX 9401315 A1	31-08-1994
			NO 940595 A	23-08-1994
			NZ 250944 A	27-02-1996
			PH 30602 A	31-07-1997
			PL 178215 B1	31-03-2000
			RU 2126002 C1	10-02-1999
			SG 52300 A1	28-09-1998
			TW 384286 B	11-03-2000
			US 5519036 A ✓	21-05-1996
			US 5612335 A	18-03-1997
			US 5827849 A	27-10-1998
			ZA 9401159 A	21-08-1995
			EE 9400311 A	15-04-1996
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WO 2004018432	A	04-03-2004	AU 2003256793 A1	11-03-2004
			EP 1539704 A1	15-06-2005
			WO 2004018432 A1	04-03-2004
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2005/000939

International filing date (day/month/year)
10.03.2005

Priority date (day/month/year)
12.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D223/16, C07D405/12, C07D401/12, C07D417/12, C07D409/12, C07D413/12, C07D403/12, C07D495/04,

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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NL-2280 HV Rijswijk - Pays Bas
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Authorized Officer

Seitner, I

Telephone No. +31 70 340-2389



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/000939

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/000939

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 7 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 7
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/000939

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-9
	No: Claims	1
Inventive step (IS)	Yes: Claims	2-9
	No: Claims	1
Industrial applicability (IA)	Yes: Claims	1-6,8-9
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 96/05194 A (DR. KARL THOMAE GMBH) 22 February 1996 (1996-02-22)

D2: EP-A-0 612 741 (DR. KARL THOMAE GMBH) 31 August 1994 (1994-08-31)

D3: WO 2004/018432 A (ELI LILLY AND COMPANY; GADSKI, ROBERT, ALAN; HIPSKIND, PHILIP, ARTHUR;) 4 March 2004 (2004-03-04)

V.1. Novelty:

Documents D1 and D2 disclose compounds (see in D1: page 76, compound (9), page 93, example 10; in D2: page 45, examples (29) and (31)) falling within the scope of the present general formula (I). Therefore, the subject-matter of claim 1 is not novel over the prior art (Article 33(2) PCT).

The compounds of claim 2 and the pharmaceutical use of compounds of formula (I) for the treatment of neurological disorders have not been disclosed in the prior art. Therefore, the subject-matter of claims 2-9 is novel (Article 33(2) PCT).

V.2. Inventive Step:

The subject-matter of claims 1-9, in as far as novel, is considered as involving an inventive

step in the sense of Article 33(3) PCT:

Document D3 is regarded as being the closest prior art the subject-matter of the present application and discloses (see page 39: example 32; page 37: example 20; page 1; claims 9-15) benzazepine derivatives which are histamine receptor antagonists for the treatment of Alzheimer disease, mood and attention adjustments, cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, narcolepsy and motion sickness.

The general formula (I) of claim 1 differs from these known compounds in that the nitrogen atom of the benzazepine ring is substituted by cycloalkyl (corresponding to the definition of R1) and the phenyl ring of the benzazepine ring is substituted by aryl, heterocyclyl, heteroaryl (corresponding to the definition of R2). In the compounds of D3 the nitrogen atom is substituted by cycloalkyl-methyl and the phenyl ring by piperidinyl-alkoxy.

The problem to be solved by the present invention may therefore be regarded as the provision of further histamine receptor antagonists for the treatment of neurological disorders.

In view of the teaching of the prior art, the skilled person had no incentive to undertake above mentioned modifications on the compounds known from D3 when searching for further histamine receptor antagonists for the treatment of neurological disorders.

Hence, the novel subject-matter of claim 1 and the subject-matter of claims 2-9 is considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of neurological diseases and the subject matter of claims 1-6 and 8-9 is therefore considered as industrially applicable (Article 33(4) PCT).

For the assessment of the present claim 7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

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in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.